THE OTHER G.M.P.: GOOD MANUFACTURING PRACTICE AND ITS IMPORTANCE IN THE VALIDATION OF CONSTRUCTED PHARMACEUTICAL FACILITIES

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The work reported is part of an ongoing PhD study prompted by the particular difficulties encountered when two very different quality cultures interact (in this case Pharmaceutical industry clients and Construction industry providers). Pharmaceutical facilities have particular needs for their production requirements. Stringent regulations are set by regulatory bodies such as the Medicines and Healthcare products Regulatory Agency (MHRA) (in the UK) and the Food and Drugs Administration (FDA) in the US. This creates special problems of quality when it comes to the commissioning, validation and hand-over of the building, as it appears to be at odds with the rather less demanding quality systems that are normally accepted in the construction sector. The aim of the research is to model an acceptable process for incorporating these stringent validation requirements into the design, procurement and construction processes. There is little or no specific academic literature on the subject, though the trades and professional press (particularly in the USA) provide some normative comment on the problem area. The main academic grounding of the research is in Systems Theory and empirical data is being collecting using a multiple case study approach. Research data was collected from a number of pharmaceutical facility construction case studies and was used to test and inform a best practice model of facility validation. The qualitative methods of participant and direct observation were used as the main information gathering tools. The paper reports on the regulatory expectations that influence the construction of projects of this type and the impact on the best practice model of validation.

Keywords: Quality, Commissioning, Validation, attitudes.

INTRODUCTION

Projects for the construction of pharmaceutical facilities differ from many construction projects because of the complex manufacturing processes housed within the facility and the critical nature of products that are produced. Tedesco & Titus (1995) suggest costs of items such as finishes, services installations, support systems, utilities and other hardware are far more significant than for non-pharmaceutical manufacturing facilities of equivalent size. Due to the nature of pharmaceutical products it is critical that the facility housing the production process complies with current regulatory requirements and performs its function perfectly from the very start of production, and even before. In order to demonstrate that facility compliance has been achieved there is a stringent validation process, and failure of the facility to

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Render, N, Greenwood, D and Edge, J (2005) The other G.M.P: good manufacturing practice and its importance in the validation of constructed pharmaceutical facilities. *In:* Khosrowshahi, F (Ed.), *21st Annual ARCOM Conference*, 7-9 September 2005, SOAS, University of London. Association of Researchers in Construction Management, Vol. 2, 917-25.

satisfy the relevant regulatory body will result in non-compliance, rendering the facility useless until it is remedied.

AIM OF THE RESEARCH

The reported research forms the early part of a PhD study. The aim of the study is to investigate the way that validation activities are currently accommodated within the process of constructing pharmaceutical facilities; to compare this with what *should* be done; and thereby to arrive at a model of best practice. In order to achieve this aim, the following paper objectives have been set:

- define what constitutes validation of a pharmaceutical facility;
- analyse the cultural views of the client and contactor in terms of project success criteria, project quality and regulatory compliance;
- examine the implementation process and identify and explain those factors that influence the success of the validation activity;
- assess what validation service provider models are commonly used and determine by the use of a research case study, the implications of the adopted approach.
- establish what validation process stages typically occur and analyse the research data to establish if there is any deviation in content and timing from the third order validation cybernetic model.

PROBLEM STATEMENT

Despite the fact that facility validation is such a crucial element of pharmaceutical projects, it is still generally treated by the building team as an after-thought, an unpleasant duty to be performed at the end of commissioning, rather than something that is central to the construction process. There is evidence of a 'clash of cultures' (Odum, 1992) that underlies the aspirations of the building's providers (designers and constructors) and those who have commissioned its use (the client).

As a result, non-compliance, expensive re-work and project delay is common, and this leads to late plant start-up, delayed production, client dissatisfaction and, in some cases, ultimately litigation. However, these problems have received little or no research attention from those concerned with construction industry processes. Wheeler (1994) underlines the significance of this by noting that how we complete and handover our buildings is as important as how we design and construct them.

The validation process is based on providing documented proof, through testing, that the installed facility and systems, that are critical to the manufacturing process, consistently operate as specified. Testing procedures and strategies adopted in the industry seem to be based on past experience and company procedure and not on theoretical concepts.

VALIDATION OF A PHARMACEUTICAL FACILITY

To determine the key reasons why pharmaceutical facilities are validated and to determine what regulatory constraints are put on the construction industry a literature review was undertaken.

The literature on facility validation is almost exclusively produced by the healthcare technology industry, which includes pharmaceutical, biological and medical device manufacturing sectors.

Various authors have recognized the effects of these regulations. De Valle (1995) suggests that factors such as plant geographical location and product market location have to be well understood to effectively manage the design, construction and validation of a pharmaceutical facility.

Allan (2004) also found that the regulations have made validation costly and time-consuming. In order to understand why these effects occur in the UK (European) and USA regulations have been analyzed, and the following sections report this analysis.

UK AND EUROPEAN REGULATIONS

The Medicines and Healthcare products Regulatory Agency (MHRA) is the UK regulatory agency responsible for ensuring that healthcare products and medical equipment meet the required standards.

The Agency is an executive arm of the Department of Health. In April 2003 the MHRA replaced the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA).

The MHRA is the Competent Authority for medical devices and the pharmaceuticals Licensing Authority. The main activities of the agency are to enforce the requirements ensuring compliance to standards of pharmaceutical manufacture.

In 1991 there was a harmonization of manufacturing authorizations and Good Manufacturing Practice (GMP) within the European Community and pharmaceutical inspections are now regulated by European Commission Directives. There are two main European Commission Directives that give the principles and guidelines of Good Manufacturing Practice (GMP). Directive 91/356/EEC gives information for medical products for human use and Directive 91/412/EEC gives information for veterinary medicinal products.

Article 8 of the Rules, Guidance for Pharmaceutical Manufacturers and Distributors (MCA, 2002) states that ‘Premises and manufacturing equipment shall be located, designed, constructed and maintained to suit the intended operations’

It goes on to say ‘Layout, design and operation must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid contamination, cross contamination and, in general any adverse effect on the quality of the product’ and ‘Premises and equipment intended to be used for manufacturing operations which are critical for the quality of the products shall be subjected to appropriate qualification’.

Qualification, or as it is also widely termed *validation* is ‘the action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results’ (MCA, 2002). The directives define those areas of specific importance as:-

1. Avoidance of material or product contamination.

2. Premises maintenance operations that do not present a hazard to the product quality.

3. Appropriate lighting, temperature, humidity and Ventilation.

4. Premises design to afford maximum protection against insects or other animals.

5. Prevention of entry of unauthorized people.

The focus of this research is primarily concerned with items 1, 2 and 3 of the directives, as these are the areas that the construction industry has most influence and control over.

The level of guidance that is given by the different regulatory authorities is general in nature and leaves the responsibility to the pharmaceutical manufacturer to provide documented evidence that the manufacturing facility is compliant with GMP. *Quality* therefore must be designed into the facilities and associated systems that will be used to produce the finished pharmaceutical drug product (Odum, 1997). The success of building in quality into a facility and hence the final drug product is dependant on the understanding of GMPs and the validation program.

SUMMARY OF GMP REQUIREMENTS

The study thus far has identified the main regulatory agencies, their expectations and their influence on the construction of pharmaceutical facilities. Building on the definitions of the validation activity the goal is therefore to provide documented proof that:

1. The premises, the facilities, the equipment and the processes have been *designed* in accordance with the requirements of current Good Manufacturing Practice (GMP). This represents the activity called Design Qualification (DQ).

2. The facilities and equipment have been constructed and *installed* in compliance with their design specifications. This represents the activity called Installation Qualification (IQ).

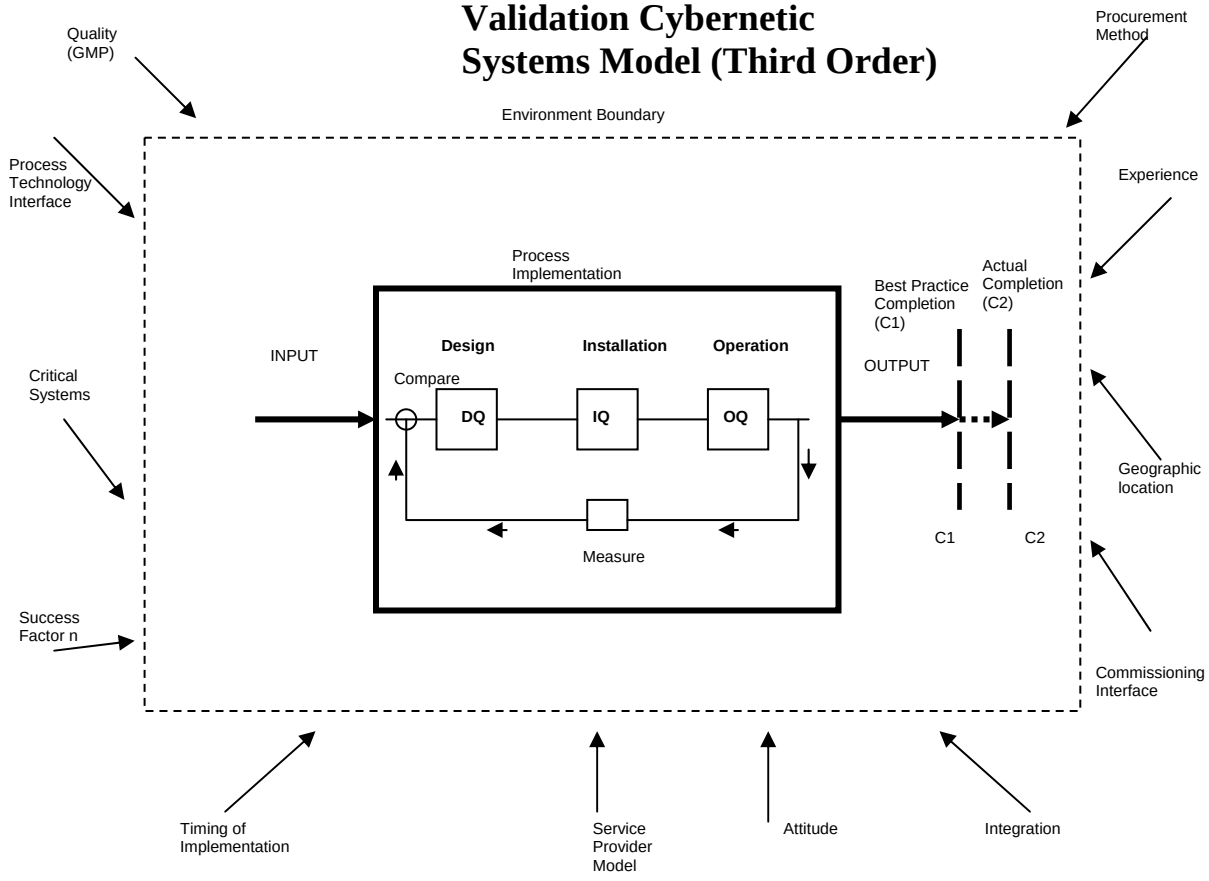
3. The facility and the equipment *operate* in accordance with their design specifications. This represents the activity called Operational Qualification (OQ).

4. The facility and equipment operate within their design specification to repeatedly and reliably *produce* a finished product of the required quality. This represents the activity called Process Qualification (PQ). It is essential that the construction and client teams operate in an integrated manner, sharing their specialist knowledge, with the common goal of regulatory compliance.

MODEL DEVELOPMENT

Together with the understanding and interpretation of the main regulatory requirements there are a number of other success related factors that will have an effect on the project outcome. The success factors at this stage are partly developed independent hypothetical propositions that may or may not be directly influential. Yin (1994), argues that each proposition directs focus on an area to be examined and each specific proposition may assist in enclosing the study within reasonable boundaries. The success factors are not exhaustive and by the process of interpretivist methods (Bryman, 1988) may lead to the generation of others. This then leads to the following model of Pharmaceutical Facility Validation (See Figure 1).

Figure 1: Validation Cybernetic System Model (Third Order)



The validation process model can be viewed as an open system. The system, of the type described by Yolles, (1999) comprises of input, a process and an output. Roper, (1994) describes open systems as having no mechanism for comparison of the output and input and are termed *black box* systems. The introduction of a feedback loop, sensor and comparator allows direct comparison of output with input. This comparison will result in the observation of deviation and is known as a *white box* system.

In the same way the validation process can be considered in similar terms where the desired system output is GMP compliance, the input is the validation test stimuli and the process is the implementation model. The introduction of a feedback loop, sensor and comparator introduce the ability to provide cybernetic control. The term cybernetic comes from the ancient Greek word Kubernesis which means ‘steering’ or ‘governing’.

To provide sufficient validation system testing coverage, black box or functional system analysis alone would not be a suitable system model. The combination of structural or white box techniques and functional analysis would provide a more suitable model.

It is recognized that the utilization of *sufficient* validation test procedures and testing concepts will be fundamental in achieving project success. Therefore, other

industries that have similar characteristics to the pharmaceutical industry (i.e. technically complex processes, with the requirement for system testing to provide assurance of project quality) have been additionally investigated in the research. The main aim is to determine if there are any highly developed testing and implementation solutions currently being used that could be applicable to the provision of pharmaceutical buildings. The open system view of validation, as part of the construction process, also leads to the system being open to the local environment at the system boundary. Success factors, as identified in figure 1, will be acting at this boundary. The negative feedback is based on circular causal chain mechanisms monitoring and feeding back information on deviations from the goal.
The model represents a sequential set of activities that are time series dependant. Each activity can only commence once the previous one is completed. Best practice project completion point is represented by C1and C2 represents the actual completion of the project in the termination phase. The deviation between C1 and C2 can be seen as the measurement of the absence of in-built quality and time delay. Allan (2004) has examined downstream problems of this type. He has found that cost can escalate and schedules can extend due to the failure of construction organization to integrate and to produce quality documentation. It is proposed that the reason for deviation from best practice is related to those factors acting at the system boundary.

RESEARCH STRATEGY

Participant Observation

Two main research strategies identified by Glaser and Strauss, (1967) are verification and generation. Verification, positivist (Easterby -Smith et al, 1991) or logico-deductive strategies relate to proposition or hypothesis testing. These are most commonly associated with empirical data that is quantitative.

Generation or interpretivist methods of research rely on allowing theory to emerge from the data; and there is a tendency for such data to be of a qualitative nature (Bryman, 1988). The nature of the study problem has *shaped* the research strategy. The limited amount of existing theory published on the subject pointed to the need to employ an almost exclusively qualitative empirical study. According to Jorgensen (1989) use of participant observation is particularly applicable to research problems where little is known about the problem being studied and the phenomenon is somehow obscured from the views of the outsider. In essence human studies require a unique methodology that allows the observer to be placed in the everyday setting of the observed. Therefore a case study was undertaken with the researcher adopting the research methodology of participant observation.

Case Study and Questionnaire

The two main data collection methods employed in the research have been:-

1. Site based participant observation, as a member of a validation team within a pharmaceutical manufacturing company's quality assurance department.

2. An industry questionnaire.

The case study project was the construction of a pharmaceutical pilot plant which comprised of a tablet compression suite, tablet coating suite and packaging hall. The data collection methods used were interviews with the construction project manager and validation manager, collection of observation notes in the form of a case study diary, memos, reports, validation protocols, letters, and informal interviews. Once the

research data was collected it was then analyzed. This was done by breaking the data into segments that were of a controllable size, that allow the identification of patterns, sequences, classes, types or processes. The analysis process then consisted of assembling the data in such a way that permitted comprehension or meaning to be derived from the data.

By piecing together the research findings in this way and making sense of them, the process of theory building or theorizing takes place. Jorgensen, (1997) describes theorizing as 'an arrangement of facts in the form of an explanation or interpretation'.

To supplement the fieldwork an industry questionnaire was sent to construction and pharmaceutical practitioners. The survey was used specifically as a sampling tool to gauge the attitudes and views of both study groups. This mixed mode research was used to help provide what Yin (1994) terms *converging lines of enquiry.*

RESULTS

Case Study Findings

The findings below are a summary of a number of generalizations that came from the site-based research: -

- Experience - The main contractor demonstrated a limited knowledge of the pharmaceutical industry. This lack of understanding stemmed from limited experience of this project type and no formal education within the subject area. It became evident that there are wide cultural difference between pharmaceutical manufacture and construction working practices.
- Service Provider Model – The validation specialist employed by the pharmaceutical client was not sufficiently experienced in construction/engineering disciplines to create suitable validation test protocols. The *specialist's* background was related to process engineering and not facility construction.
- Validation Process – The client failed to appoint the validation specialist until after construction had commenced. This resulted in problems associated with the sequencing of validation tasks.
- Risk – The main contractor viewed the validation works as specialist and therefore an area of high financial risk. This view was based partly on previous experience of providing validation assistance as an un-charged extra.
- The commissioning activity became the project phase for carrying out nearly all of the validation works. The commissioning and validation teams did not work as an integrated team and expensive re-witnessing tests were required.
- Regulatory expectations – Those involved appeared to be unclear of levels to be achieved. The team member who had the greatest experience in this area was the client validation manager. Unfortunately, the validation manager was not part of the *core* project group.
- Communications – Project progress meetings were too time consuming and were attended by too many different disciplines. As a result it became difficult for the main contractor to progress the project whilst waiting for specific issues and problems to be addressed.

- Some Good Manufacturing Practice issues were not included in the initial project design and they were not discovered until after project completion. The main reason for this was that a design review exercise was not carried out.

The main problems associated with timing and implementation that have informed the third order cybernetic systems model have been identified as:-

1. Incomplete and unsuitable User Requirement Specification (URS).

2. Inadequate resultant Functional Specification (FS).

3. Absence of a Validation Master Plan (VMP).

4. Missing validation process stages.

5. Non-sequential validation process.

6. Validation process occurring post construction project.

7. Change control – inability to accommodate project change and prevention of post project GMP non-compliance.

CONCLUSIONS

The criteria by which the success of any construction project is judged are normally time, cost and quality. Time and cost are readily measurable, but the meaning of quality can be more elusive, and this is at the root of the problem of successful validation of pharmaceutical buildings. During the research, it has become clear that construction project managers probably tend to understand quality as a measure of workmanship, while pharmaceutical project managers view it in terms of assurance and regulatory compliance. This difference in understanding and the importance of the construction project managers input into the validation activity has been overlooked or at best underestimated.

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